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October 6, 2005

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 03P-0064/CP1 – Comments in Opposition to Aventis Pharmaceuticals Citizen Petition Supplement on Enoxaparin Sodium Injection.

Dear Sir or Madam:

On February 19, 2003, Aventis Pharmaceuticals ("Aventis"), through its counsel, filed the above-referenced citizen petition requesting that the Food and Drug Administration ("FDA") "withhold approval of any abbreviated new drug application ("ANDA")" for enoxaparin sodium ("enoxaparin"). Aventis markets this product under the trade name Lovenox®. On September 26, 2005, Aventis filed a second supplement to its Citizen Petition (the "Citizen Petition Supplement"). Amphastar hereby responds.

As demonstrated by this response, Aventis continues to submit to the docket new information regarding certain as yet undefined "structural fingerprints" to which it attributes speculative clinical significance, and which Aventis believes may be process-dependent. These submissions of additional information are not based on valid scientific evidence relevant to whether a generic applicant can show equivalence to Lovenox under

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the applicable regulatory criteria. Instead, the Citizen Petition Supplement (as well as Aventis' previous submissions to the docket) are designed to inappropriately forestall FDA review of pending ANDAs for enoxaparin. Further, the Citizen Petition Supplement's critique of the chromatograms provided by Amphastar to FDA in its July 18, 2005 submission to this docket is both inaccurate and misleading. In fact, the chromatograms provided by Amphastar demonstrate that its enoxaparin product is similar to Lovenox® in all key respects.

I. The "Newly Discovered Biological Properties of Enoxaparin" Are Irrelevant To A Review Of An ANDA For This Product And Are Not Supported By Valid Scientific Evidence of Clinical Significance.

In part one of its Citizen Petition Supplement, Aventis continues to speculate on the clinical significance of various "newly discovered features" of Lovenox, without providing any scientifically valid evidence. To support its argument, Aventis submitted four recent reports of *in-vitro* studies, which it claims demonstrate the clinical relevance of particular characteristics of Lovenox's chemical structure. FDA has made it clear that variations in chemical structure do not preclude "a 'sameness' finding for purposes of 21 U.S.C. § 355(j)," unless they are "significant for the product's intended uses." [1] All along, Aventis has been unable to do more than merely speculate as to any such clinical significance, and the four new *in-vitro* studies do not change this fact. Indeed, the conclusions of the study reports make it clear that the results are, at least in part, preliminary and do not establish any clinical significance at all. See, e.g., Citizen Petition Supplement Appendix A: Preliminary Data ("Additional studies are needed to define the role of 1, 6 anhydro on CRP-mediated suppression of endothelial TFPI."); and Appendix

B: Conclusions and Perspectives (Page 17) (listing four additional studies that would be required "for a complete description and comparison of the oligosaccharides effect on the blood coagulation process").

In its original Citizen Petition, Aventis argued, among other things, that presence of the 1, 6 anhydro ring structure in the appropriate concentration was key to the clinical effectiveness of enoxaparin. FDA approved a supplemental NDA filed by Aventis, which revised the Lovenox labeling to include the 1,6 anhydro ring structure on the reducing end of 15 to 25% of the product's polysaccharide chains.[2] Amphastar took steps to ensure that its generic enoxaparin met this criterion. Indeed, any generic enoxaparin product would be required to conform to the updated labeling in order to obtain FDA approval. Here, the Citizen Petition Supplement's discussion of the clinical relevance of other enoxaparin fractions is not supported by the information provided. Instead, the discussion reflects continued speculation by Aventis regarding the characteristics of its product, which is irrelevant to a determination of whether a generic version of enoxaparin is equivalent to Lovenox® under the applicable ANDA review criteria.

Further, Aventis continues to stress the significance and dependence of its manufacturing process on the clinical effectiveness of Lovenox®. Aventis continues to

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1 Serono Lab. v. Shalala, 158 F.3d 1313, 1317 (D.C. Cir. 1998).

2 See Approval letter for Aventis's supplemental NDA, 20-164/S-055, which provided "additional characterization and new structural information on the active ingredient of the drug product, enoxaparin sodium" (July 23, 2004).

argue that a generic applicant must use the same manufacturing process as the innovator to obtain approval. Aventis's reasoning is flawed. Provided that a generic manufacturer's product conforms to the current labeling, and is bioequivalent to the innovator drug, it proves the point: the same manufacturing process is not required to produce a product that is the same as the innovator's. Duplicating an innovator's manufacturing process is not required by law and is not the standard for demonstrating sameness.

II. Amphastar's Chromatograms Demonstrate That Its Enoxaparin Product Is Chemically Equivalent To Lovenox®.

Amphastar's earlier response, dated July 18, 2005, (hereinafter "Amphastar Response") demonstrates that the two products, Amphastar's proposed generic enoxaparin and Aventis' Lovenox, have similar chromatographic profiles. This is demonstrated by the entire distribution chromatogram (Fig.1 in the Amphastar Response) and the enzyme-hydrolyzed chromatogram (Fig. 2 in the Amphastar Response).

In part two of Aventis's Citizen Petition Supplement, it attempts to discount the Amphastar Response. As outlined below, all of Aventis's comments are incorrect or misleading. We hereby respond to those comments:

1. Regarding 1,6-Anhydro Ring

FDA approved a change to Lovenox's approved labeling in July 2004, to include in the specifications the 1,6-anhydro ring on the reducing end of 15 to 25% of the

product's polysaccharide chains. Amphastar has no objection to a requirement that every generic enoxaparin meet the same specification.

2. Regarding "the Sameness"

Aventis states: *"even if Amphastar's chromatograms of its product were identical to chromatograms of enoxaparin, this would not establish 'sameness' as required by FDA."* Citizen Petition Supplement at Page 10.

Amphastar has never planned to establish the "sameness" of the two products based only on chromatograms. Amphastar has established the "sameness" through comparison or characterization of many items, in accordance with FDA requlations.

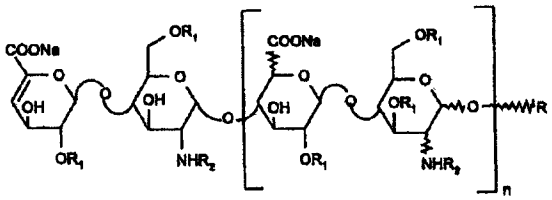
3. Regarding an Impurity Peak (Peak-29)

Aventis states: *"Amphastar's Lovenox chromatogram contains a peak at 29 minutes not present in Amphastar's chromatogram of its own product."* Citizen Petition Supplement at Page 13.

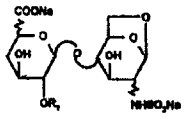
This statement is true, but it is irrelevant because the peak at 29 minutes represents an impurity.

As we have reported to FDA, the peak at 29 minutes in Fig. 1 (the Lovenox chromatogram) of the Amphastar Response has been proven to be a disaccharide Δ1s. As is well-known and stated in the Lovenox package insert (copy provided as Appendix 1), enoxaparin has the following structure:

Figure 1: Structural Formula (Reprinted from Appendix 1).



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	X*= 15 to 25%		[redacted]
	100 - X	H	[redacted]

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

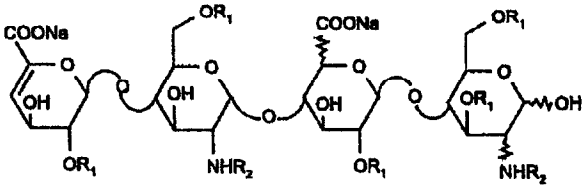
The smallest meaningful oligosaccharides for both types of reducing end, as stated in Lovenox package insert, are

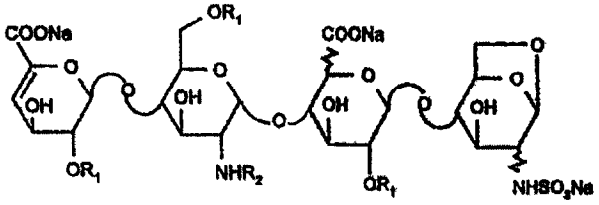
(1) smallest n=1 for non-1,6-anhydro ring structure at the reducing end; and

(2) smallest n=0 for 1,6-anhydro ring structure at the reducing end.

The structures for the two smallest oligosaccharides are as follows:

Figure 2: (Reprinted from Appendix 1).





Both types of the smallest oligosaccharides in enoxaparin are tetrasaccharides. Thus, disaccharides are not included as a meaningful component of Lovenox in the structural formula identified in the product's FDA-approved labeling. As a result, disaccharides are not only irrelevant to the structure of Lovenox, they are impurities.

Therefore, Peak-29 in the Lovenox chromatogram is **an impurity.** This impurity peak does not appear in the chromatogram of our product. FDA encourages a generic drug to have lower levels of impurities than contained in the listed reference drug. Furthermore, all drug manufacturers are responsible for minimizing the amount of impurities in drug products. See Guidance for Industry, ANDAs: Impurities in Drug Substances, (Nov. 1999).

4. Regarding an Impurity Peak (Peak-8.5)

Aventis states: *"The Lovenox sample shows a clear peak at 8.5 minutes that is observed only as a very minor peak in Amphastar's sample of its own product."*

This is also true, but not relevant.

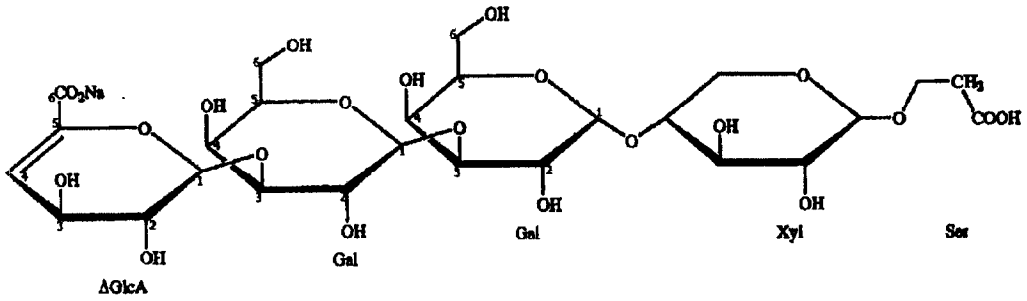
The peak at 8.5 minutes (hereinafter "Peak-8.5") appears for the Lovenox sample between disaccharide Peak ΔIVa and disaccharide Peak ΔVIs.

As reported by a patent application assigned to Aventis (Application No. US2005/0119477 A1, hereinafter "Application '477 " copy provided as Appendix 2), the peak, denoted as Peak 3 in Fig. 1 of Application '477, was identified as

$$\Delta GlcA\beta_{1\text{-}3}\, Gal\, \beta_{1\text{-}3}\, Gal\beta_{1\text{-}4}\, Xyl\, \beta_1\text{-}O\text{-}CH_2\text{–}COOH$$

(page 5 of Application '477), and has the following structure:

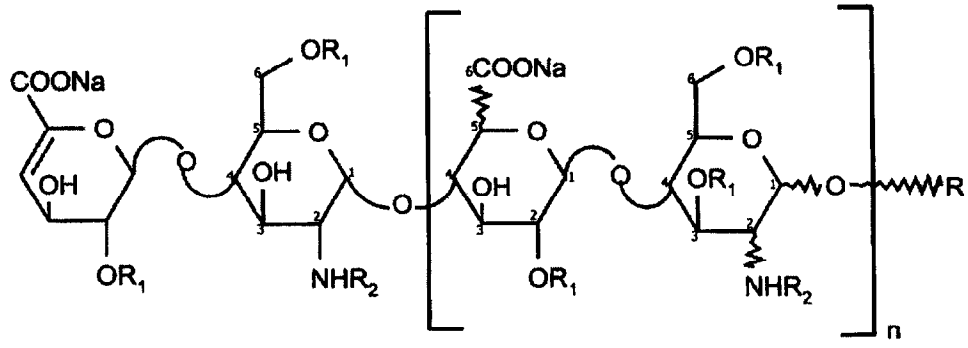
Figure 3 (Reprinted from Appendix 2).



Therefore, the first three saccharide units in this tetrasaccharide are 1,3- linked. Namely, the number 1 carbon atom of a saccharide unit is linked, through an ether bond (C-O-C), with number 3 carbon atom of its right-adjacent saccharide unit.

However, the Lovenox labeling (Appendix 1) and the European Pharmacopeia (Appendix 3) clearly indicate that all meaningful oligosaccharides in enoxaparin are 1,4-linked:

Figure 4 (Reprinted from Appendix 1).



Namely, number 1 carbon atom of a saccharide unit in enoxaparin is always linked,

through an ether bond (C-O-C), with number 4 carbon atom of its right-adjacent saccharide unit.

Thus the Peak-8.5 is irrelevant to enoxaparin because it is also **an impurity.**

5. Regarding Peak Heights of Chromatograms

Aventis also indicates in its Citizen Petition Supplement (pages 13 and 15) that in comparing the two products, certain peaks have different heights. Specifically, Aventis makes this observation with regard to the peaks at 39, 40, 41, 42, 54, and 55 minutes (hereinafter "Peaks 39 to 55").

This difference in heights is not surprising and has no relevance to a determination of whether the two products are equivalent for purposes of generic approval. Enoxaparin is a mixture of oligosaccharides. The specifications for enoxaparin have acceptable ranges to allow for some fluctuation in various product characteristics, for example:

(1) Acceptable range of average molecular weight:

The specification for average molecular weight of enoxaparin is 3500 to 5500 daltons (see European Pharmacopeia, EP-1097, copy provided as Appendix 3). The maximum allowed relative difference for average molecular weight could be as high as **57%** [57%=(5500-3500)/3500 X 100%].

(2) Acceptable range of ratio of Anti-factor Xa to Anti-factor IIa:

The specification for the ratio of Anti-factor Xa to Anti-factor IIa of enoxaparin is 3.3 to 5.3 (see EP-1097, Appendix 3). The maximum allowed relative difference for the

ratio of Anti-factor Xa to Anti-factor IIa could be as high as **61%** [61%=(5.3-3.3)/3.3 X100%].

(3) Acceptable range of molecular weight distribution (< 2000 daltons):

The specification for molecular weight distribution of a species with a molecular weight of <2,000 daltons is less than or equal to 20%, as indicated by the Lovenox package insert. The maximum allowed relative difference for the molecular distribution (for <2,000 daltons) could be actually infinity [infinity =(20%-0%)/0% X100%]. This specification means the amount of all components with molecular weights less than 2,000 daltons in enoxaparin could be as low as zero.

The molecular weights of all tetrasaccharides and hexasaccharides in enoxaparin are less than 2,000 daltons. In fact, the molecular weight of the heaviest possible sequences of hexasaccharides in enoxaparin is 1,995 daltons.

As we have identified and reported to the FDA, all peaks at 39 to 55 are tetrasaccharides or hexasaccharides.

Based on the specifications indicated by Aventis, and as discussed above, the tetrasaccharides are impurities. The product specifications require that these lower molecular weight species (<2,000 daltons) be present as concentrations of less than 20% and as little as zero. Thus, at the extreme, peaks for components falling within this low molecular weight range could even be eliminated from the drug product without impact on safety and efficacy. In fact, the heights for peaks at 39 to 55 of the two products are quite similar, and are certainly within the acceptable ranges included in the specifications for enoxaparin.

III. Aventis' Continued Submissions To The Docket Unfairly Delay Legitimate Generic Competition.

Since submission of its Citizen Petition in February 2003, Aventis has been arguing to delay legitimate generic competition. Each time Amphastar addresses a concern, e.g., the 1-6, anhydro ring structure, Aventis simply drums up another. Such delays are exactly what has prompted FDA Chief Counsel Sheldon Bradshaw to seek public input on how best to reform the citizen petition process to ensure that it does not result in inappropriate delay of generic competition. See The Pink Sheet Daily (Sept. 19, 2005) ("I've been considering whether or not we can implement something that would allow the agency to point out for all the world to see when citizen petitions are specious, untimely or otherwise appear intended to hamper or delay competition.") (quoting Mr. Bradshaw's remarks at the Generic Pharmaceutical Association's first Annual Policy Conference in Washington, DC). Indeed, delaying the availability of generic enoxaparin would be against public policy and inconsistent with legislative intent. In enacting the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Waxman-Hatch" amendments), a primary objective of Congress was to ensure availability of affordable generic products for the benefit of consumers. Congress "intended to encourage competition by decreasing the time and expense of bringing generic drugs to market, and thereby to provide the public with low cost drugs."[3]

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[3] See 54 Fed. Reg. 28,872, 28,874 (Jul. 10, 1989) (emphasis added).

For the reasons above, as well as those in Amphastar's previous submissions to this docket, Amphastar respectfully requests that the Food and Drug Administration deny the actions requested by Aventis in Citizen Petition 2003P-0064.

Very truly yours,

Stephen A. Campbell, Esq.
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